SCIENTIFIC ABSTRACT

Background

BHT-3009 is an antigen-specific immunotherapy agent in development as a treatment of the autoimmune disease relapsing remitting multiple sclerosis (MS). The product is designed to suppress inflammatory autoimmune responses to myelin basic protein (MBP), one of the key self-antigens targeted in MS.

BHT-3009 is a plasmid expression vector that encodes full-length human myelin basic protein (hMBP) under the control of the cytomegalovirus immediate-early promoter/enhancer. When BHT-3009 is administered by intramuscular injection, low-level expression of hMBP protein occurs for a period of two to four weeks at the injection site and also within cells that traffic to draining lymph nodes. This limited expression of a self-antigen in a novel immunological context has been found to attenuate ongoing autoimmune responses in mouse and rat models of experimental autoimmune encephalomyelitis (EAE), the preclinical model for MS.

In studies in the SJL/J mouse model of EAE, plasmid DNA expression vectors encoding myelin autoantigens significantly reduced the severity of induced disability and the frequency of relapses. Treatment reduced the numbers of antigen-specific γ-interferon secreting T cells present in lymph nodes and suppressed auto-antibody responses to spreading epitopes.

Recent studies by several laboratories suggest that atorvastatin and other members of this class of drugs, collectively known as statins, may have anti-inflammatory properties that may be beneficial in treating multiple sclerosis. Statins reduce the production of pro-inflammatory mediators such as iNOS, TNF-alpha, MHC class II expression, matrix metalloprotease and ICAM-1 (CD54). In the SJL/J model of EAE, atorvastatin contributed to the efficacy of an expression vector encoding a myelin auto-antigen. Combination therapy significantly reduced mean disability scores relative to appropriate control groups treated in parallel.

Study Design

The study presented in Protocol BHT-3009-01 is a multi-center, randomized, double-blind, dose-escalation, placebo-controlled trial to evaluate the safety of immunotherapy with BHT-3009 when given alone or when combined with atorvastatin in patients with MS.

Three dose levels of BHT-3009 will be administered, with ten patients being treated at each level. Patients will be randomized to treatment with BHT-3009 plus atorvastatin, BHT-3009 plus atorva-placebo, or BHT-placebo plus atorva-placebo. Over 13 weeks, patients receive four intramuscular injections of BHT-3009 or BHT-placebo and take two atorvastatin or atorva-placebo tablets daily. After treatment and follow-up evaluations are complete, the study will be unblinded and patients who had received placebo will be re-randomized to a treatment with BHT-3009 alone or to BHT-3009 in combination with atorvastatin for an additional 13-week period. Thus, all patients who participate in the study will receive treatment with BHT-3009.